



The Warburg hypothesis and weak ELF biointeractions

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ABSTRACT

The Warburg observation concerning ATP generation in cancer cells is analyzed with regard to the likely involvement of H⁺ resonance effects on the angular velocity of the ATP synthase rotor. It is reasonable to expect that the variety of diseases associated with mitochondrial dysfunction may in part be related to the ATP synthase rate of rotation. Experimental measurements of ATP synthase rotational rates, as found in the literature, are consistent with what might be expected from the ion cyclotron resonance (ICR) frequencies of protons moving under a Lorentz force determined by the approximate surface intensity of the geomagnetic field (~26-65 μ T). One research approach proposes that applying the electronic sum of two critical multiple resonance frequencies simultaneously may serve to more closely resemble real world biochemical changes as compared to applying these frequencies sequentially. Accordingly, it is suggested that applying the sum of the two individual resonance frequencies corresponding to H⁺ and H₃O⁺ has the capacity to both increase proton density as well as couple to ATP synthase rotation. Not only will this tend to stabilize the F₀ rotational rate but also perhaps make it feasible to control this rate, thereby providing a new and potentially efficacious means of treating diseases connected to mitochondrial dysfunction electromagnetically.

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Introduction

It has long been known (Warburg et al. 1924) that the energy currency for cancer cells is obtained from a different source than normal cells. As a rule ATP is generated by the proton gradient across the inner mitochondrial membrane, making convenient use of the rotating enzyme ATP Synthase (ATPS) (Boyer 1997) embedded within this membrane. The ATP Synthase enzyme consists of two connected parts: F₀ embedded in the inner mitochondrial membrane, and F₁, located within the mitochondrial interior. Warburg observed that cancer cells bypass the ATPS step, instead merely using the oxidation of glucose (glycolysis) to provide its ATP. This is counterintuitive because in so doing cancer cells fail to make use of the more highly efficient ATP Synthase mechanism.

Recently, there has been increasing discussion (Epstein et al. 2017; Esparza-Molto and Cuezva 2018; Jiang et al. 2015; Moreno-Sanchez et al. 2014; Pokorny et al. 2017; Sullivan and Chandel 2014) concerning the relevance of Warburg's observation to cancer production and/or treatment. This, despite the fact that the Warburg Hypothesis tells us nothing about the cause of cancer cells, but merely how their energy content is derived. Nevertheless the possibility exists that the

inefficient rate of ATP inclusion in cancer cells may reflect problems with ATP Synthase itself. This in turn might conceivably implicate ATPS dysfunction as a reason for mitochondrial-linked disease, and perhaps even as a potential contributing factor to oncogenesis.

In the following we suggest a new approach to this question, reframing Warburg in terms of the effects of ELF bioelectromagnetic fields on ATP Synthase function, more specifically on whether ion cyclotron resonance (ICR) coupling to ATPS exists and to what extent this possibility might carry implications for disease and/or treatment. In part this proposed new approach is based on recent experiments (D'Emilia et al. 2015; Novikov et al. 2016; Zhadin et al. 1998) that found positive ICR responses in various biosystems following tuning for glu⁺, H₃O⁺, and heavier cations. Prior to this, ICR experimental trials had focused on transport ions such as Ca²⁺, K⁺, and Mg²⁺ (Liboff et al. 1987; Smith et al. 1987; Thomas et al. 1986). For this older work it was felt that an ICR response was at least partially reasonable in that one could posit a non-zero Lorentz force acting on ions with finite velocities related to their signaling properties. However the more recent ICR studies has found that more massive cations, not specifically involved in transport/signaling, are also sensitive to ICR tuning, making it unlikely that

the ICR coupling process is limited solely to the Lorentz force acting on transport ions in motion.

Weak ELF biointeractions

Among the more recent ELF experimental studies are those initiated by Grimaldi (D'Emilia et al. 2015) involving water structure. Exposing water to ICR field combinations tuned to the hydronium ion (H_3O^+) results in a sharply reduced pH, or equivalently, in an increase in uncoupled protons. Additionally, a series of experiments in Novikov's laboratory (Novikov and Fesenko 2001) have probed the use of ICR signals in teasing apart various metabolic reactions. Especially interesting is that this laboratory has found it particularly useful to simultaneously apply different ICR frequencies corresponding to more than one cation by simply applying the electronic sum of the various signals. Presumably the system to which this summed signal is being applied is "smart enough" to respond to each of the ICR conditions that comprise the electronic sum. In so doing it is hoped that the system under study will correspond more faithfully to real-world biochemical changes, which occur either simultaneously or in rapid succession. In a loose comparison, the Novikov application of several ICR frequencies at once might be considered equivalent to taking a diverse group of pharmaceutically prescribed pills together.

Key role of ATP synthase

The ATP Synthase complex, embedded in the mitochondrial inner membrane, consists of a rotational part, F_0 , and a second component, F_1 . The F_0 rotary component binds hydrogen ions from the low pH region external to the inner membrane, but within the outer membrane. The binding of these protons provide the first step in the eventual generation of ATP, which is finalized in the second component F_1 . The rotary component is quite interesting in that its angular velocity is such as to rapidly bind successively available hydrogen ions, thereby allowing the generation of ATP at very high rates. Clearly then, since ATP is vital to complete cellular expression, the high rate of rotation for ATP synthase plays an important role in matters of well-being. At first glance the higher this rate the greater the likelihood of cellular vitality. A larger rate should also result in increased ATP production, and, in general, reduce problems related to aging. Greater rates of ATP production might be expected to be beneficial for those suffering heart failure. And, most interestingly, it is conceivable that precise control of the F_0

rotation rate as an independent variable may be of value in further understanding of ATPS function.

Indeed It is conceivable that impaired ATP Synthase rotary motion can play an important role in various problems related to mitochondrial dysfunction, including, for example, effects on the immune system (Weinberg et al. 2015), heart failure (Neubauer 2007), senescence (Correia-Melo and Passos 2015), neurological disease (Schapira 1998), cancer (Esparza-Molto and Cuezva 2018), and metastatic progression (Santidrian et al. 2013). Thus, the general question arises as to the biological consequences attached to the rotary frequencies that are found for F_0 during ATP production. In short, it may be very biologically interesting to explore the potential relation of the speed of rotation of F_0 to mitochondrial disease.

Central to ATPS function is the question of ATP demand, where cells in sudden need of extra energy, whether due to working, exercising, or thinking, can send signals to their mitochondria requesting more ATP (Koebsmann et al. 2002). It is interesting to note that the ATPS rotational rate appears to be independent of the nature of cell demand, functioning solely in an on/off manner.

Weak ELF magnetic fields and ATP synthase

We draw attention to the possibility that the rotation rate in ATP synthase may be functionally related to the geomagnetic field (GMF). This is in part suggested by the fact that the F_0 unit described above entails the curvilinear motion of a charged particle, the same situation that follows the Lorentz force on a moving charged particle in a magnetic field. By itself, this fact might be considered simply as an interesting similarity, but the possible involvement of the GMF is made more plausible when one realizes that the observed rotation rates for F_0 are consistent with the rotational frequencies specifically expected for protons in motion in magnetostatic fields comparable to GMF surface intensities.

To show this we can obtain the ICR frequencies for a single proton in a constant magnetic field whose intensity ranges from 25 to 65 μT , the approximate worldwide range of absolute surface intensities due to the GMF. The proton has a charge to mass ratio of $95.76 \times 10^6 \text{ Coul/kg}$. Making use of the expression for the cyclotron resonance frequency $2\pi f = qB/m$ of a charged particle with charge to mass q/m in a magnetostatic field B , one finds this frequency as a function of the magnetostatic field, or in terms of the ratio of ICR frequency to magnetostatic field intensity $f/B = 15.24 \text{ Hz}/\mu\text{T}$. This enables us, using the 25–65 μT range of values for the GMF, to find the expected range of resonance frequencies for thermal protons due to geomagnetic coupling, namely 381 to 991 Hz.

This can be compared to the experimentally observed values for ATPS rotation, averaging 351 Hz with maximum rates of 671 Hz in one configuration and 721 Hz in another (Ueno et al. 2005; Vinothkumer et al. 2016).

Proposed experimental approach

Consistent with trying to either maintain or increase the rate of ATP generation we therefore seek to devise experiments that can electromagnetically control the rotational speed of ATP Synthase. Note that It is beyond the scope of this paper to detail the actual means of detecting ATP changes that might be determined in any of the various laboratory methods (Shi et al. 2017) that have been reported. Instead we focus solely on the electromagnetic parameters.

One can identify two key cationic components of the ATP Synthase sequence, both involving protons, that may be readily stimulated using ICR, and therefore contribute to this angular velocity. First, there are the protons derived from the water molecules in the space between the inner and outer mitochondrial membranes that are due to be eventually bound to one of the multiple sequential sites on F_0 . To achieve a sufficient number of available protons from this surrounding region it is necessary that the available water in this area has a relatively low pH. It has been established (D'Emilia et al. 2015) that the pH of water exposed to the H_3O^+ combined resonance field is sharply lowered, resulting in an excess of free protons. Thus the first of the two experimentally interesting proposed resonance conditions, corresponding to the ICR frequency for the hydrogen ion, will have the effect of enhancing the number of hydrogen ions in the region between the inner and outer mitochondrial membranes, thus enhancing the probability of binding protons by F_0 .

We have already mentioned the second region in the ATPS complex that may be responsive to proton stimulation, namely the set of proton binding sites on F_0 . There is considerable uncertainty concerning the details surrounding this binding process. One simple-minded approach is to assume that as each proton is bound, there is a rotation of F_0 , allowing the next sequential proton binding site to be made available. This ensuing rotational motion corresponds to what one would expect from a freely moving proton in a constant magnetic field whose intensity corresponds to the proton cyclotron resonance, as determined from the charge to mass ratio of the proton. In a crude description of what happens one can imagine that as each successively attached proton is bound by F_0 , it will then move in a circular path determined by the Lorentz force.

These two resonance conditions, for H_3O^+ and H^+ , will necessarily enjoy a common magnetostatic field. We can make a reasonable estimate of the two resonance frequencies for these ions by assuming this static field to be 50 μT , i.e., about halfway within the 25–65 μT range of surface intensities. The resonance frequencies for this specific magnetostatic field intensity are 762 Hz for H^+ and 40.4 Hz for H_3O^+ . These two resonance frequencies can be applied as one signal, namely the electronic sum with the total peak magnetic intensity set arbitrarily at 100 nT.

Given these basic parameters, investigators will be enabled to seek optimal exposures as well as explore more efficacious exposures, e.g., applying the individual H^+ and H_3O^+ ICR signals solely and sequentially instead of in combination.

Discussion

The work presented here, although admittedly speculative, is at the same time of some significance. To the best of our knowledge, no one has yet discussed the key importance of the ATPS rotational rate, nor elaborated on possible means of controlling this rate. This, despite the fact there is considerable evidence linking a variety of diseases to mitochondrial dysfunction. Clearly, given the importance surrounding the proper delivery of ATP and the remarkably high rotational rates involved in this process, it is difficult to avoid concluding that defects in this system may have serious consequences.

We note the rotation rates described in the literature, specifically the approximate maximum and average rates respectively, 700 Hz and 350 Hz. As pointed out above, one can readily associate the higher value with the expected resonance frequency of protons exposed to GMF surface intensities. But the lower frequency, regarded as an average value in experimental reports, may also carry extra physical significance. Again, at GMF intensities this frequency corresponds closely to that of the H_2^+ cation, instead of the single proton. This fact may be interpreted in two possible ways, first to mean that the binding to F_0 can occur at a higher rate, where two protons are bound simultaneously. Less likely It can also mean that the H_2^+ ion itself can be directly bound by the ATPS rotor. In any event, the underlying charge sequence concerning this lower frequency can readily be probed experimentally using the ICR frequency corresponding to H_2^+ .

The present work, in effect, relates energy demand in biological systems to the local geomagnetic field. This generalization is consistent with the recent conclusion by the author (Liboff 2019) that the GMF plays a far more important role in biology than previously

thought. However there remains the key question as to the details surrounding the putative Lorentz force interaction between the local geomagnetic field and the protons that are bound to the F_0 rotor. Does the Lorentz force act on the protons before or after they are bound? If before, then we can imagine a process where ATP generation is maximized when the intrinsic rotational frequency for F_0 matches the proton resonance frequency. If, instead, the protons are first bound to the F_0 binding sites, this would imply that the rotor frequency is set by the ICR frequency.

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